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ART UNIT	**PAPER NUMBER**
1647	

NOTIFICATION DATE	DELIVERY MODE
03/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/573,262	KOGA ET AL.	
	Examiner	Art Unit	
	JON M. LOCKARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-4,7-13 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23/06, 11/7/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Alignments*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 5-6, 14, and 19, in the reply filed on 20 November 2007 is acknowledged. Applicant's election of SEQ ID NO:18 encoded by SEQ ID NO:19) in the reply filed on 20 November 2007 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-4, 7-13, and 15-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 20 November 2007.

3. The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

4. The response filed on 20 November 2007 has been entered in full. Claims 1-4, 7-13, and 15-18 are withdrawn from further consideration as discussed *supra*. Therefore, claims 1-19 are pending, and claims 5-6, 14, and 19 are the subject of this Office action. It is noted that the elected invention is the polypeptide of SEQ ID NO:18, and the claims have been examined to the extent that they read upon the elected invention.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file, and the Examiner has acknowledged that "all" copies of the certified copies of the priority documents have been received in this National Stage

application. However, should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign applications should be submitted under 37 CFR 1.55 in reply to this action.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 23 March 2006 and 07 November 2007 have been considered by the examiner.

Drawings

7. The Drawings are objected to for the following informalities:

8. The drawings are objected to because Figures 1, 6, 8, 9, 10, and 13 disclose amino acid sequences without an accompanying sequence identifier (i.e., SEQ ID NO: #). The SEQ ID NO: may be inserted into the Figure or the Brief Description of the Drawings.

9. Figures 3A, 8, 9, and 10 are objected to because 37 CFR 1.84 states that "[P]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter".

10. Figures 4B, 4C, 6 and 8 are too dark for the Examiner to reasonably interpret.

11. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should *not* be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement

sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

12. The abstract of the disclosure is objected to because it is more than one paragraph in length. See MPEP § 608.01(b). Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. Appropriate correction is suggested.

13. The disclosure is objected to because of the following informalities:

14. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example pg 3, lines 14-15). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

15. The use of the trademarks has been noted throughout the Specification (See for example GATEWAY™ (pg 25, line 1), BIOSOURCE™ (pg 64, line 36), and HI-TRAP™ (pg 82, lines 6-7). Trademarks should be capitalized wherever they appear and should be accompanied by the generic terminology. Applicant is encouraged to review and make appropriate corrections to the specification regarding the misuse of trademarks. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. Appropriate correction is suggested.

16. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant is requested to avoid the use of "novel" in the title, as patents are presumed to be novel and unobvious. Appropriate correction is suggested.

Claim Objections

17. Claim 5 is objected to because of the following informalities: Claim 5 encompasses non-elected inventions, e.g., SEQ ID NO:1 and SEQ ID NO:15. Appropriate correction is suggested.

18. Claims 6 and 14 are objected to for depending from a withdrawn claim.

19. Claim 19 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 5. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the recitation of, "An angiogenesis inhibitor which contains one of polypeptide of (a) or (b) as an active ingredient" in the preamble of the claim has been interpreted as an intended use, thus the claims are substantially duplicative. It is noted that if Applicant intended to claim a composition, amending the claim to recite, for example, "A composition comprising…" would be remedial.

Claim Rejections - 35 USC § 101

20. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

21. Claim 5 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed compound (a polypeptide) is not "isolated". The claim encompasses, for example, a polypeptide that has not been removed from the animal or human. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claim should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP 2105.

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

22. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 5-6, 14, and 19 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated protein consisting or comprising the amino acid sequence SEQ ID NO:18, does not reasonably provide enablement for (1) an isolated polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18; (2) a polypeptide comprising the full-length or a part of an amino acid sequence derived from an amino acid sequence represented by SEQ ID NO:18 by deletion, substitution or addition of a part of the amino acids having a biological activity substantially equivalent to a polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18; (3) a polypeptide comprising whole or a part of the amino acid sequence identical or substantially identical to the amino acid sequence represented by SEQ ID NO:18; or (4) a polypeptide comprising whole or a part of the amino acid sequence which is derived from the amino acid sequence represented by SEQ ID NO:18, by deletion, substitution, or addition and has a biological activity substantially equivalent to a polypeptide comprising whole or a part of the amino acid sequence identical or substantially identical to the amino acid sequence represented by SEQ ID NO:18. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

24. The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

25. The claims are drawn quite broadly to (1) an isolated polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18; (2) a polypeptide comprising the full-length or a part of an amino acid sequence derived from an amino acid sequence represented by SEQ ID NO:18 by deletion, substitution or addition of a part of the amino acids having a biological activity substantially equivalent to a polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18. The claims also recite wherein the polypeptide is a recombinant protein generated in a host cell, and a kit comprising the polypeptide. The claims also recite an angiogenesis inhibitor which contains a polypeptide as an active ingredient, wherein the polypeptide (a) comprises whole or a part of the amino acid sequence identical or substantially

identical to the amino acid sequence represented by SEQ ID NO:18; or (b) comprises whole or a part of the amino acid sequence which is derived from the amino acid sequence represented by SEQ ID NO:18, by deletion, substitution, or addition and has a biological activity substantially equivalent to a polypeptide comprising whole or a part of the amino acid sequence identical or substantially identical to the amino acid sequence represented by SEQ ID NO:18. While the Specification discloses a protein comprising the amino acid sequence SEQ ID NO:18 which inhibits angiogenesis, it does not teach a commensurate number of the claimed polypeptides. Other than the polypeptide of SEQ ID NO:18, the disclosure fails to provide sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims. The disclosure has not shown (1) which portions of the protein of SEQ ID NO:18 are critical to the angiogenesis inhibiting activity of the protein of SEQ ID NO:18; (2) what modifications e.g., substitutions, deletions, or additions) one can make to SEQ ID NO:18 that will result in protein mutants or variants with the same function/activity as the protein of SEQ ID NO:18; and (3) any guidance on how to use the variants of SEQ ID NO:18 which would, based on the language of said claims, encompass both active and inactive variants, especially in the absence of any structural or functional limitations in the claims. The state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions.

26. The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and

DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions and still retain the activity of the protein of SEQ ID NO:18.

27. Although the Specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of the active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, that may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone

(Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; cited by Applicant).

28. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

29. Furthermore, it is noted that the Examiner has interpreted claim 6 as reading on the production of the polypeptide in the context of (1) isolated host cells in culture to produce the encoded protein recombinantly, (2) genetically engineered host cells to express such products in vivo for use in gene therapy, and (3) expression in transgenic animals.

30. The specification teaches that the DNA of the invention can be introduced and expressed in the patient by gene therapy using a suitable vector (see pg 38, lines 6-9). However, there are no methods or working examples disclosed in the instant application that indicate the claimed nucleic acid is introduced and expressed in a cell or organism for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or the subject, or in what

quantity and duration. Gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A.J., J. Pharm. Pharmacol. 53: 1169-1174, 2001; see abstract; See also Palù et al. J. Biotechnol. 68:1-13, 1999). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.J.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease.

31. The Specification also asserts that the gene encoding the polypeptide can be inserted into animal cells for the purpose of producing a transgenic animal (See pg 26, lines 6-36). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated gene is demonstrated to express the encoded claimed polypeptide. The unpredictability of the art is very high with regard to making transgenic organisms. For example, Wang et al. (Nuc. Acids Res. 27:4609-4618, 1999) surveyed gene expression in transgenic animals and found each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the

original gene (See pg 4617). Likewise, Kaufman et al. (Blood 94:3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9%) to "intermediate" to "none", due to factors such as vector poisoning and spontaneous structural rearrangements (See pg 3180, col. 1; pg 3182-3183). Additionally, the Specification discloses that a possible technique to introduce the claimed transgene into animals includes microinjection. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome, which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod. Fert. Dev. 6:585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events.

32. Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed fusion protein and to introduce the claimed nucleic acid in the cell of an organisms for therapy; the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid into the cell of an organism to be able to produce the encoded protein, the absence of working examples directed to the same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organisms cells; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

33. Please note that this issue could be overcome by amending claim 6 to recite, for example, "… generated in an isolated host cell… ".

Claim Rejections - 35 USC § 112, 1st Paragraph (Written Description)

34. Claims 5-6, 14, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

35. Claims 5-6, 14, and 19 are drawn quite broadly to (1) an isolated polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18; (2) a polypeptide comprising the full-length or a part of an amino acid sequence derived from an amino acid sequence represented by SEQ ID NO:18 by deletion, substitution or addition of a part of the amino acids having a biological activity substantially equivalent to a polypeptide comprising the full-length or a part of an amino acid sequence which is the same or substantially the same as an amino acid sequence represented by SEQ ID NO:18. The claims also recite wherein the polypeptide is a recombinant protein generated in a host cell, and a kit comprising the polypeptide. The claims also recite an angiogenesis inhibitor which contains a polypeptide as an active ingredient, wherein the polypeptide (a) comprises whole or a part of the amino acid sequence identical or substantially identical to the amino acid sequence represented by SEQ ID NO:18; or (b) comprises whole or a part of the amino acid sequence which is derived from the amino acid sequence represented by SEQ ID NO:18, by deletion, substitution, or addition and has a

biological activity substantially equivalent to a polypeptide comprising whole or a part of the amino acid sequence identical or substantially identical to the amino acid sequence represented by SEQ ID NO:18. Thus, the claims are drawn to a genus of polypeptides that are defined only by a partial structure.

36. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure. There is not even identification of any particular portion of the structure that must be conserved.

37. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one protein species (SEQ ID NO:18) is not adequate written description of an entire genus of functionally equivalent polypeptides, which incorporate all variants, derivatives, and homologs encompassed by the claims.

38. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

39. With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

40. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

41. Therefore, only an isolated protein comprising/consisting the amino acid sequence SEQ ID NO:18, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd Paragraph

42. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

43. Claims 5-6, 14, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

44. Claims 5 and 19 are rejected as indefinite for reciting the phrase "represented by". Without knowing whether the limitation refers to a protein consisting of the amino acid sequence of SEQ ID NO:18, a protein corresponding to SEQ ID NO:18, or a protein typified by SEQ ID NO:18 (and to what degree, structurally and/or functionally), the metes and bounds of the claim cannot be determined. It is noted that for purposes of examination, the Examiner has interpreted the claims as reading on variants, derivatives, homologs, and orthologs of SEQ ID NO:18.

45. Claim 5 is rejected as being indefinite for reciting the phrase "substantially the same". Since neither the art nor the Specification provides an unambiguous definition of the phrase, the metes and bounds of the claims cannot be determined. The discussion of "substantially identical" at pg 21 of the Specification is noted, but fails to breathe life and meaning into the phrase "substantially the same", and thus the metes and bounds of the claim cannot be determined.

46. Claims 5 and 19 are rejected as being indefinite for reciting the phrase "biological activity substantially equivalent". Since neither the art nor the specification provides an unambiguous definition of the term substantially equivalent, the metes and bounds of the claim cannot be determined. The discussion of such at pg 21 of the Specification is noted but vague,

fails to breathe life and meaning into the term and thus is insufficient to render the claims definite.

47. Claim 14 is rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is considered indefinite because a kit, by definition, must contain 2 or more elements and the interrelationships between the elements must be explicitly stated (see In re Venezia 530 F.2d 956 CCPA 1975).

48. Claim 6 is rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

49. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

50. Claims 5, 14, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by van der Zwaag et al. (Developmental Dynamics. 225:336-343, published online 03 October 2002; previously cited by Examiner).

51. van der Zwaag et al. teach a PLEXIN-D1 (PLXND1) polypeptide (See Fig. 1) that comprises an amino acid sequence that shares 92% sequence identity to SEQ ID NO:18 of the

instant application (See attached sequence alignment). It is noted that the Examiner has broadly interpreted the claims as reading on variants, derivatives, homologs, and orthologs of SEQ ID NO:18 (See 112(2) rejections *supra*). It is noted that the Examiner has interpreted the claim 14 as consisting of the polypeptide of claim 5 since the "kit" recited in the claim does not comprise any other elements. Furthermore, it is noted that the recitation in claim 20 of, "An angiogenesis inhibitor which contains one of polypeptide of (a) or (b) as an active ingredient" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Thus, the van der Zwaag et al. reference meets all the limitations of claims 5, 14, and 19.

52. Claims 5, 14, and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Duke-Cohan et al. (Accession Number Q68HV1, 11 October 2004).

53. Duke-Cohan et al. teach a mouse plexin D1 polypeptide that comprises an amino acid sequence that shares 99.9% sequence identity to amino acid residues 72-1337 of SEQ ID NO:18 of the instant application (See attached sequence alignment). It is noted that the Examiner has broadly interpreted the claims as reading on variants, derivatives, homologs, and orthologs of SEQ ID NO:18 (See 112(2) rejections *supra*). It is noted that the Examiner has interpreted the claim 14 as consisting of the polypeptide of claim 5 since the "kit" recited in the claim does not

comprise any other elements. Furthermore, it is noted that the recitation in claim 20 of, "An angiogenesis inhibitor which contains one of polypeptide of (a) or (b) as an active ingredient" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Thus, the polypeptide disclosed by Duke-Cohan et al. meets all the limitations of claims 5, 14, and 19.

Claim Rejections - 35 USC § 103

54. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

55. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

56. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over van der Zwaag et al. as applied to claims 5, 14, and 19 above, and further in view of Ausubel et al. (Protein Synthesis, in Ausubel et al. (Eds.) Short Protocols in Molecular Biology (Chapter 16). New York:Wiley. 1995).

57. The teachings of van der Zwaag et al. are summarized above. The reference of van der Zwaag et al. does not teach said polypeptide recombinantly produced from a host cell in which the DNA encoding it was introduced.

58. However, such teachings are common in the art. For example, Ausubel et al. teach the use of polynucleotides operably linked to a promoter sequence, transformed into a host cell, and used to make the encoded protein (See pages 16.1-16.5 and 16.58-16.60). It would have been obvious to a person of ordinary skill in the art to use the methods of Ausubel et al. to link the polynucleotides of van der Zwaag et al. to a promoter sequence and to transform said polynucleotides into a host cell and express and purify the encoded protein. Since van der Zwaag et al. disclose that the gene encoding the polypeptide set forth in Figure 1 is a candidate gene in the genetic defect Möbius syndrome 2, one would be motivated to use the methods of Ausubel et al. to produce the encoded protein taught by van der Zwaag for biochemical characterization of the protein and to make antibodies, and it is well known in the art to place any desired cDNA sequence into an expression vector and host cell, and express the encoded protein for antibody production, ligand-binding studies, and screening for therapeutic ligands, for example. The expectation of success is high as placing polynucleotides into a vector,

transforming said vector into a host cell, and producing and isolating the encoded protein are common in the art.

59. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

60. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duke-Cohan et al. as applied to claims 5, 14, and 19 above, and further in view of Ausubel et al. (Protein Synthesis, in Ausubel et al. (Eds.) Short Protocols in Molecular Biology (Chapter 16). New York:Wiley. 1995).

61. The teachings of Duke-Cohan et al. are summarized above. The reference of Duke-Cohan et al. does not teach said polypeptide recombinantly produced from a host cell in which the DNA encoding it was introduced.

62. However, such teachings are common in the art. For example, Ausubel et al. teach the use of polynucleotides operably linked to a promoter sequence, transformed into a host cell, and used to make the encoded protein (See pages 16.1-16.5 and 16.58-16.60). It would have been obvious to a person of ordinary skill in the art to use the methods of Ausubel et al. to link the polynucleotide encoding the mouse plexin D1 polypeptide (Accession Number AY688678) of Duke-Cohan et al. to a promoter sequence and to transform said polynucleotides into a host cell and express and purify the encoded protein. One of ordinary skill in the art would be motivated to use the methods of Ausubel et al. to produce the encoded protein taught by Duke-Cohan for biochemical characterization of the protein and to make antibodies, and it is well known in the art to place any desired cDNA sequence into an expression vector and host cell, and express the

encoded protein for antibody production, ligand-binding studies, and screening for therapeutic ligands, for example. The expectation of success is high as placing polynucleotides into a vector, transforming said vector into a host cell, and producing and isolating the encoded protein are common in the art.

63. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Summary

64. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Manjunath N. Rao, Ph.D.**, can be reached on **(571) 272-0939**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon M. Lockard, Ph.D.
February 14, 2008

/Jon M Lockard/
Examiner, Art Unit 1647